

ABSTRACT OF THE DISCLOSURE

The present invention highlights the role of acetyl-CoA carboxylase through its product malonyl-CoA in regulating fatty acid
5 oxidation and synthesis, glucose metabolism and energy homeostasis. It discloses transgenic mice with inactivating mutations in the endogenous gene for the acetyl-CoA carboxylase 2 isoform of acetyl-CoA carboxylase. Inactivation of acetyl-CoA carboxylase 2 results in mice exhibiting a phenotype of reduced malonyl-CoA levels in
10 skeletal muscle and heart, unrestricted fat oxidation, and reduced fat accumulation in the liver and fat storage cells. As a result, the mice consume more food but accumulate less fat and remain leaner than wild-type mice fed the same diet. These results demonstrate that inhibition of ACC2 acetyl-CoA carboxylase could be used to regulate
15 fat oxidation and accumulation for purposes of weight control. The instant invention provides a useful animal model to regulate malonyl-CoA production by ACC2 in the regulation of fatty acid oxidation by muscle, heart, liver and other tissues. They also identify potential inhibitors for studying the mechanisms of fat
20 metabolism and weight control.